

REMARKS/ARGUMENTS

Claims 45-47, 49, 50, 58, 59, 61 and 62 are currently under examination. Claims 48, 52-56, 63, 64 and 65 are currently withdrawn. Claims 45, 46 and 63-65 have been amended herein to include clarification "persistent." Support for these amendments can be found at least at page 3, line 14 of the Specification, as filed.

Applicants thank the Examiner for the withdrawal of prior rejections and address the rejections made in the Action as follows.

Claim Rejections Under 35 U.S.C. § 103

The Examiner has rejected Claims 45-47, 49, 50, 58, 59, 61 and 62 under 35 U.S.C. § 103(a) as being obvious over **WO'257** (PCT Publication No. WO 2003/068257) in view of **Huber** (Cancer Research 40:3484-90).

At page 3 of the Action, the Examiner acknowledges that the WO'257 fails to teach immune system cycling, or to suggest a method including monitoring or analyzing steps for the purpose of understanding the dynamics of the immune system cycling (as required, for example, by step ii) of claim 45). However, at page 4 of the Action, the Examiner states that other teachings in the art indicate that those of ordinary skill in the art would have expected the presence of such immune system cycling. The Examiner cites *Huber* as teaching the cycling of the immune system between periods of cytotoxic and suppressor cell activity for this teaching. The Examiner argues that, in view of the knowledge of such cycling in the art, it would have been obvious to those of ordinary skill in the art, from the teachings of WO'257, that monitoring for a sufficient period of time to determine the dynamics of the immune system cycling could be performed so that such knowledge could be used to aid in determining when to most advantageously administer agents inhibiting suppressor/regulator cell production or activity (e.g. to aid in the prediction of when the numbers/activity or suppressor cells targeted by the anti-suppressor cell agents is likely to occur). Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, (1) the prior art reference (or references when combined) must teach or suggest all of the claim limitations; (2) there must be some reason, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; and (3) there

must be a reasonable expectation of success. M.P.E.P. § 2143. The Examiner has the burden of establishing a prima facie case of obviousness. Furthermore, a conclusion of obviousness requires that the reference(s) relied upon be enabling in that they put the public in possession of the claimed invention. M.P.E.P. § 2145.

As noted by the USPTO Examination Guidelines in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007): “In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have *reasonably* expected to have been able to do in view of that knowledge.” See Examination Guidelines at 57527, third col., first full paragraph. (emphasis added).

Applicants submit that one skilled in the art, at the filing date of the instant application, would not have reasonably been expected to combine and modify the cited references to arrive at the currently-claimed invention.

Neither WO’257, nor *Huber*, either alone or in combination, teach or suggest “cycling” of the immune system. The Examiner has already acknowledged that WO’257 fails to teach immune system cycling. *Huber* also does not teach cycling of the immune system. The data described by *Huber* only suggest a *biphasic* immune response following administration of cancerous cells to a mouse. As described by *Huber*:

“When spleen cells from the tumor-bearing mice were assayed for cytotoxicity to the MTM tumor, the immune response could be divided into 3 distinct phases (Chart 1): (a) an early cytolytic phase first detected 4 days after tumor inoculation and persisting until Day 8; (b) a noncytolytic phase commencing approximately on Day 9 and lasting until Days 13 to 16; and (c) a second cytolytic phase beginning at about 14-16 days and persisting *until the death of the animal*. The periodicity and magnitude of the immune response were independent of the initial tumor dose.” *Huber*, at page 3488, column 1, lines 9, emphasis added.)

Huber concludes that the cellular immune response in rats “can be divided into 3 sequential phases: an early cytolytic phase; a period of noncytotoxicity; and a second or late cytolytic phase” (See *Huber*, at page 3488, column 2, Discussion, lines 1-4) and “Fischer rats immunized i.p with . . . tumor cells develop a *biphasic* cytolytic response to the tumor in spleen. The first early cytolytic phase, detected within 4 days of tumor inoculation, peaks on Day 7 and decreases

by Day 9. The second (late) cytolytic phase, detected 13 or more days after tumor injection and is maintained until death.” (*Huber*, at page 3484, column 1, Abstract, lines 3-7)

This biphasic immune response reported in *Huber* is distinct from the phenomenon of immune system cycling described in the present application. The present application teaches that the immune system cycling occurs “on a *regular* basis” and further explains that this is an “oscillating persistent” immune response. (See Specification as filed, page 3, lines 6-15. See also, Figures 4-7, and 8-11 showing acute phase markers fluctuations in patients Mrs. OM and Mrs. FO.) As explained in the description of the drawings, Figures 4 and 5 show a distinct and persistent oscillation in the fluctuations of acute phase markers. (See, the specification as filed at page 11, line 35-36; and page 12, line 4-5)

The persistent or repeating nature of the “cycling” of immune response described in the instant application is neither taught, nor suggested by *Huber*. On the contrary, *Huber*’s teaching regarding maintaining the cytolytic phase until death clearly teaches away from any expectation that monitoring and analyzing the immune system data would establish a persistent cycling that could be used to determine an advantageous time to administer future patient treatments.

In the interest of advancing prosecution, Applicants have amended Claims 45, 46 and 63-65 to clarify the persistent nature of the immune system cycling that is clearly distinct from the biphasic immune response described by *Huber*. Applicants reiterate that neither of the cited references teach or suggest this persistent immune system cycling.

Additionally, neither of the cited references teach or suggest the steps of the instant claims directed to: 1) monitoring a patient for a period of time representing at least one cycle of the immune system; 2) analyzing the results to understand the dynamics of the persistent immune system cycling within the patient; and, 3) based on an understanding of the dynamics of the cycling of the immune system, administering an agent or determining when the agent is to be administered, in the treatment of a patient.

The Examiner already acknowledges that WO’257 fails to suggest methods that include monitoring and analyzing patient data for the purpose of understanding the dynamics of the immune system cycling. Applicants also submit that *Huber* does not teach or suggest such method. In particular, *Huber* does not teach or suggest monitoring a patient for a period of time representing at least one cycle of the immune system and analysing the results to understand the

dynamics of the persistent immune system cycling within the patient. Furthermore, *Huber* contains no disclosure related to administering an agent for treating the patient based on the cycling of the immune system. On the contrary, *Huber* raises doubts about the potential for therapeutic intervention based on the observation of the biphasic immune response in concluding that:

“[t]he existence of autoregulatory feedback control raises questions about the feasibility of altering specific immune responses in patients with cancer by immunotherapy regimens such as If such inocula serve to induce anti-receptor antibody and suppressor cells, the therapeutic effort may be self-defeating.” (*Huber*, page 3489, second column, final paragraph)

Thus, neither of the cited references, either alone or in combination, teach or suggest all of the limitations of the currently-pending claims. Applicants submit that one skilled in the art, reviewing the combination of *Huber* and WO’257, at the time of filing the instant application, would not have been put in possession of the full method of the currently-pending claims and would not have had a reasonable expectation of successfully combining and modifying these references to arrive at the claimed invention. In light of these comments and amendments, Applicants respectfully request withdrawal of this rejection based on the combination of *Huber* and WO’257.

Obviousness type Double Patenting:

The Examiner has maintained the rejection of Claims 45-47, 49, 50, 58, 59, 61 and 62 as being unpatentable over claims 27, 33-35, 37, 38 and 45-47 of co-pending U.S. Patent Application No. 10/503,794.

The Examiner has also maintained the rejection of Claims 45-47, 49, 50, 58, 59, 61 and 62 as being unpatentable over claims 1-4, 6, 10-13 and 15 of copending U.S. Patent Application No. 12/233,369.

Applicants respectfully submits that these provisional obviousness-type double patenting rejections will be addressed at such time that claims of the instant application and the co-pending patent applications cited by the Examiner have been found allowable. As this is not currently the status of any claims in the instant or the co-pending patent applications, Applicant requests that this rejection be held in abeyance.

Appl. No. 10/576,981

Amdt. dated March 30, 2010

Reply to Office Action having Mailing Date: December 1, 2009

Based upon the foregoing, Applicant believes that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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